Factor VIII levels and bleeding according to factor 8 mutation in pregnant carriers of haemophilia A: a multi-centre retrospective cohort study

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Introduction

Haemophilia A is an X-linked bleeding disorder leading to a deficiency of coagulation factor VIII (FVIII). Carriers can present with a wide degree of FVIII levels although median levels are 0.60 IU/mL compared with 1.02 IU/mL in non-carriers (1). FVIII levels are known to increase during pregnancy and while FVIII levels for carriers of haemophilia A increase during pregnancy, they remain lower than would be expected for non-carriers (2). The aim of this retrospective cohort study was to investigate the effect of factor 8 (F8) genotype on third trimester factor VIII levels for haemophilia A carriers and to examine the incidence of primary post-partum haemorrhage (PPH).

Methods

We conducted a retrospective cohort study of heterozygous carriers of haemophilia A seen at the Oxford Haemophilia and Thrombosis Centre between January 2011 and August 2019. Baseline, first trimester, third trimester, and postpartum (at least six weeks post-delivery) factor VIII levels were collected and patients were stratified according to the severity of the underlying mutations. The severity of the underlying mutations was also compared to the incidence of primary PPH (blood loss ≥500 mL within 24 hours after birth) and severe primary PPH (blood loss ≥1000 mL within 24 after birth).

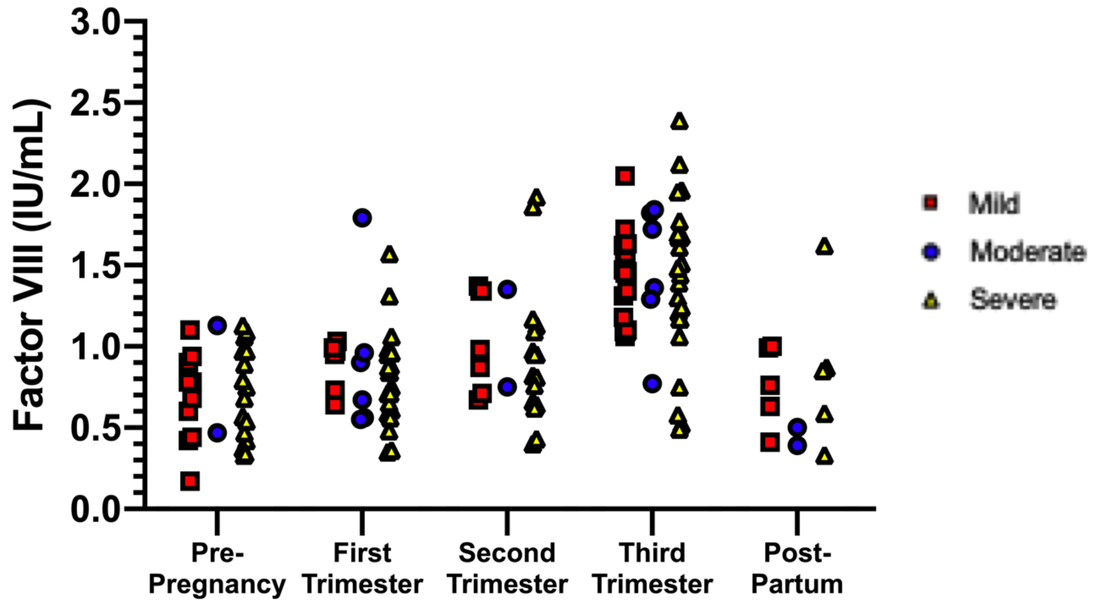

Figure 1. Factor VIII levels in carriers of mild, moderate and severe haemophilia A throughout pregnancy. Blood results available for 28 women pre-pregnancy, 32 in the first trimester, 25 in the second trimester, 46 in the third trimester and 12 post-partum. Postpartum was defined as more than six weeks post-delivery..

Patient Characteristics	
Number of patients	52
Mean baseline factor VIII (standard deviation)	0.73 (0.25) IU/mL
Severity of familial haemophilia	
mild	16 (30.8%)
moderate	8 (15.4%)
severe	28 (53.8%)
Mutation type	
missense	27 (51.9%)
nonsense	2 (3.8%)
frameshift	6 (11.5%)
splice site change	2 (3.8%)
intron 22	13 (25.0%)
other large structural change	2 (3.8%)
Pregnancy Characteristics	
Number of pregnancies	64
Parity	
Nulliparous	29
Para 1	23
Para 2	6
Para 3	1
Unknown	5
Median age at delivery (range)	29 (17 - 39) years
Mode of delivery	
vaginal	23 (35.9%)
Caesarean section	18 (28.1%)
termination of pregnancy	1 (1.6%)
not yet delivered	6 (9.4%)
data not available	16 (25.0%)
Primary postpartum haemorrhage†	18 (42.9%‡)

† Defined as blood loss ≥500 mL within 24 hours postpartum
‡ Of 42 patients where blood loss data is present

Results

The mean baseline FVIII level was 0.73±0.25 IU/mL. This rose to a mean third trimester level of 1.40±0.41 IU/mL. There were no significant differences in FVIII levels between carriers of mild, moderate and severe haemophilia A (Figure 1). FVIII levels at baseline were 0.78±0.22 IU/mL for mild, 0.83±0.33 IU/mL for moderate, and 0.70±0.25 IU/mL for severe (p=0.53). Mean FVIII levels during the third trimester were 1.42±0.28 IU/mL for mild, 1.47±0.41 IU/mL for moderate, and 1.37±0.49 IU/mL for severe (p=0.90).

The overall incidence of primary PPH was 18/42 (42.9%), including three (7.1%) with a severe primary PPH . PPH occurred in 14/25 (56.0%) carriers of severe haemophilia A and 4/14 (28.6%) carriers of mild haemophilia A. Estimated blood loss ranged from 150 mL to 1650 mL with a median of 400 mL (300 – 650 mL). FVIII levels did not significantly differ between groups with and without a primary PPH either at baseline (0.70±0.30 IU/mL with and 0.76±0.24 IU/mL without, p=0.53) or during the third trimester (1.52±0.49 IU/mL with and 1.41±0.39 IU/mL without, p=0.42). Bleeding data were available for only three carriers of moderate haemophilia A, none of whom had a primary PPH.

Poor Factor Response

Four patients had baseline FVIII less than 0.50 IU/mL and third trimester FVIII less than 1.00 IU/mL. These patients were heterozygous for the following mutations:

- F8 c.681G>T (p.Trp227Cys) - results in a severe phenotype.
- F8 c.601+1 G>T (splice site change) - results in a severe phenotype.
- F8 c.516C>G (p.Cys172Trp) - results in a severe phenotype.
- F8 c.800G>A (p.Cys267Tyr) - results in a moderate phenotype.

3 of the 4 mutations described are missense mutations in the F8 A1 domain. Overall 3/15 (20%) pregnancies in women with an A1 domain mutation had a poor factor VIII increment compared to 1/28 (4%) for other mutations.

Conclusion

This retrospective cohort study investigated the association between factor 8 genotype severity and factor VIII levels during pregnancy for 52 heterozygous carriers of mild, moderate or severe haemophilia A (64 pregnancies) . There were no significant differences in factor VIII levels for carriers of mild, moderate or severe haemophilia A at baseline or in the third trimester (mild 1.42±0.28 IU/mL; moderate 1.47±0.41; severe 1.37±0.49; p=0.90). Post-partum haemorrhage rates were higher for carriers of severe haemophilia A (13/24; 54.2%) compared to carriers of mild haemophilia A (4/14; 28.6%).

References

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